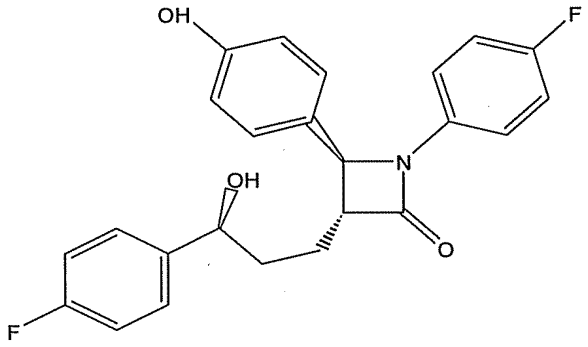
REMARKS

The Office Action of February 25, 2008 has been reviewed and the comments therein carefully considered. Claims 1, 35-37, 42, 45, and 47 are pending in this application. Claims 4-10, 12-17, 21-34, 38-41, 46, and 48 have been withdrawn by the Examiner. Claims 2, 3, 11, 18-20, 43-44, and 46 were canceled, without prejudice to the filing of one or more divisional or continuation applications.

Each of these pending claims stands finally rejected under 35 U.S.C. § 103(a) as being obvious over Rosenblum et al. (EP 0 720 599) and Ullah (WO 99/47123) in view of Frei (Proc. Soc. Exp. Biol. Med. 1999 Dec; 222(3): 196-204). This rejection is respectfully traversed.

In embodiments set forth in claims 1 and 47, Applicants have discovered compositions and combinations comprising:

(a) 0.1 to 1000 milligrams of a sterol absorption represented by Formula (II):



(II)

or pharmaceutically acceptable salts or solvates thereof; and

(b) 1 to 1000 milligrams of aspirin.

In the Office Action of August 27, 2003, Applicants were required to elect a species of sterol absorption inhibitor, blood modifier, and third therapeutic agent. In a Response dated September 9, 2003, Applicants provisionally elected with traverse ezetimibe, which is represented by Formula (II) above. In the same Response, Applicants provisionally elected with traverse aspirin as the blood modifier and simvastatin (an HMG CoA reductase inhibitor) as the third therapeutic agent.

The claimed compositions, combinations, and treatment methods can be useful for treating vascular conditions and/or lowering concentration of a sterol in plasma in a mammal (page 72, lines 13-18 of the specification).

Rosenblum disclose the compound of Formula II (ezetimibe) at page 29, Ex. 6. Rosenblum disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum (Ex. A and B Page 29). Rosenblum teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims).

Ullah discloses the use of a combination of aspirin for reducing the risk of a myocardial infarction and a statin (such as simvastatin) for lowering cholesterol and preventing or treating atherosclerosis, in combination (page 1, lines 14-18). Ullah discloses unique arrangements of these two compounds, such as in the form of a bi-layered tablet, to minimize the unfavorable drug interactions between statins and aspirin (page 2, line 32 to page 3, line 10).

Frei discloses that antioxidants may inhibit atherogenesis and improve vascular function by two different mechanisms (Abstract). Lipid-soluble antioxidants present in LDL, such as vitamin C, can inhibit LDL oxidation (Abstract). Antioxidants present in the cells of the vascular wall decrease cellular production and release of reactive oxygen species (ROS), inhibit endothelial activation and improve the biologic activity of ENDO (Abstract).

The Office Action continues to assert that the claimed compositions are obvious due to the combined teachings of Rosenblum, Ullah, and Frei. Specifically, it is proposed that one skilled in the art would find it obvious to combine the ezetimibe/statin composition of Rosenblum with the aspirin/statin composition of Ullah to arrive at the claimed ezetimibe/aspirin composition. It is further proposed that one of ordinary skill would have been motivated to additionally include an antioxidant, such as vitamin C, in view of the teachings of Frei. The rationale advanced to explain why such a combination would be obvious is based on the case of *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), where, based on the facts, the court determined that combining two compositions each of which is taught as useful for the same purpose to form a third composition useful for the very same purpose is presumptively obvious. *Kerkhoven* at 1072.

However, *Kerkhoven* does not represent the definitive test of obviousness. The true test of obviousness is "whether the teachings of the prior art, *taken as a whole*, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991) (emphasis added). The facts of *Kerkhoven* merely presents one situation where the court found this obviousness standard to have been met. However, because the facts of the instant case are distinguishable from those in *Kerkhoven*, simply relying on the holding of *Kerkhoven* to establish a case of obviousness is inappropriate.

In *Kerkhoven*, the applicant was attempting to patent a process of preparing a detergent composition comprising several ingredients. *Id.* at 1070-71. The claimed process required forming two detergent solutions, each comprising the same ingredients in different amounts, and mixing the two solutions together to form the final detergent composition. *Id.* The court found that this process was *prima facie* obvious because the applicant was merely combining two solutions, each a known detergent, to form another detergent comprising all of the ingredients of the precursor solutions. *Id.* at 1072. Thus, *Kerkhoven* involved the combination of two known compositions, in their entirety, to form another composition made up of the same components and directed to the same purpose as each of the prior art compositions individually.

The Office Action has attempted to analogize the instant case to the facts in *Kerkhoven* by stating that the claimed compositions are merely a combination of the compositions of Rosenblum, Ullah, and Frei, each of which is directed to the purpose of lowering cholesterol. However, this attempt fails to properly explain the distinctions between the facts of *Kerkhoven* and the instant case.

According to Ullah, aspirin itself does not have any cholesterol-lowering properties. Aspirin is disclosed in Ullah as being used to reduce the risk of a myocardial infarction while *statins* are described as responsible for any cholesterol lowering effects (page 1, lines 14-18). Ullah only describes co-administration of aspirin and statins because it is not uncommon for a patient suffering from high cholesterol to also be at risk for a myocardial infarction (page 1, lines 18-20). Based on this information, Ullah proposes a combination of statin and aspirin arranged so as to limit potential drug interactions between them. Therefore, Ullah does not teach the use of aspirin and statin, in combination, as a cholesterol-lowering agent. Rather, Ullah teaches a way in which a cholesterol-lowering statin can be safely co-

administered with a myocardial-infarction-preventing aspirin. The therapeutic "use" or "purpose" of Ullah's composition then is really twofold: lowering cholesterol and reducing the risk of a myocardial infarction. In contrast, the use or purpose of the claimed composition, like the composition of Rosenblum, is to reduce cholesterol levels. Thus, *Kerkhoven* is distinguishable since the "combinable" compositions are directed to divergent purposes.

While Ullah may be relevant in providing a motivation to combine a statin and ezetimibe, which are directed to similar purposes, this does not explain why one skilled in the art would combine aspirin and ezetimibe. Nothing in Ullah requires the administration of the statin in combination with aspirin to get the therapeutic cholesterol lowering effect. Consequently, presuming one skilled in the art would find it obvious to combine ezetimibe and aspirin because the prior art teaches that each of these agents is used in compositions useful for the same purpose is erroneous. "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Hedges*, 783 F.2d 238, 241 (CCPA 1965).

Furthermore, the proposed combination of references would result in a composition that includes compounds not recited in the subject claims. While Applicants admit that these claims include the transitional word "comprising," and thus may be open to the addition of other components other than those specifically recited in the claims, this does not eliminate the Examiner's burden of establishing why the prior art compositions would be combined. Rather, a finding of obviousness still requires that there be some rationale for combining the prior art compositions, as a whole, in the amount disclosed therein. *Ex Parte El-Naggar*, 2007 WL 2814131 (BPAI, Sept. 20, 2007). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

In *El-Naggar*, the applicants claimed a composition for treating inflammatory disorders comprising a COX-2 inhibitor, low dose aspirin, and an antioxidant. *El-Naggar* at *1. The claim was rejected as obvious over several prior art references. *Id.* at *2-3. The

primary reference taught the use of a COX-2 inhibitor to treat inflammatory disorders but did not mention aspirin or an antioxidant. *Id.* at *2. Another reference taught that a composition which included cod liver or linseed oil, vitamins A and E, and a low dosage of aspirin was excellent in treating inflammatory disorders. *Id.* A third prior art reference taught that antioxidants, in combination with amine derivatives of benzoic acid, could treat inflammatory conditions. *Id.* In making the obviousness rejection, the examiner cited *In re Kerkhoven* for the proposition that it was obvious to combine the ingredients recited in the claim since each was taught by the prior art as being useful for the same purpose. *Id.* at *2.

On appeal the Board, in reversing the rejection, cautioned against rejecting a composition claim by merely picking and choosing various components from known compositions in lieu of considering the prior art references as a whole. *Id.* at *3. In the Board's opinion, one skilled in the art reading the cited art as a whole would have reasoned that the therapeutic effects of those compositions could only be obtained by addition of many ingredients in addition to those recited in the claim. *Id.* at *4.

The Board also made note of the fact that the claim, by using the transitional word "comprising," could also include other ingredients in addition to those ingredients specifically recited in the claim. *Id.* However, the Board stated, "[t]he Examiner has not adequately explained why one of ordinary skill would have included all of the different ingredients required in the prior art compositions, in the quantities disclosed in the prior art, in a single composition as recited in [the claim]." *Id.*

Thus, the fact that the claims do not include components that would be present upon a combination of the prior art cannot be disregarded because the claims include the transition "comprising." Rather, there must be some showing that one skilled in the art would find it obvious to combine the prior art references as a whole and that such a combination would result in the claimed composition.

Assuming for the sake of argument that a *prima facie* case of evidence has been established, evidence of secondary considerations of nonobviousness, such as unexpected results, can be submitted to rebut the *prima facie* case.

In the last Office Action, Applicants set forth a detailed explanation of their surprising findings that co-administering aspirin and ezetimibe to a subject had an effect on Arachidonic acid (AA) induced platelet aggregation far superior than a treatment regime of

aspirin or ezetimibe alone. (December 4, 2007 Response, page 3-5). This finding led to the conclusion, supported by the Declarations of Dr. Davis and Dr. Chintala, that combining aspirin and ezetimibe produced a synergistic effect on the ability of each of these compounds to inhibit platelet aggregation. *Id.*

The Office Action asserts that this evidence of unexpected results is not persuasive because it is not commensurate with the scope of the claim. (February 25, 2008 Office Action, page 5). Specifically, the Office Action takes issue with the fact that Applicants have only shown results with respect to rats treated with 100 mg/kg aspirin and 3 mg/kg/day ezetimibe while the claimed composition comprises ezetimibe in the range of 0.1-1000 mg and aspirin in the range of 1-1000 mg. According to the Office Action, there is no rationale as to how the dosage of aspirin or ezetimibe, and the unexpected benefits of co-administration, can be expanded to such a broad range.

However, Applicants believe that the test data, in conjunction with the Declarations of Dr. Davis and Dr. Chintala, is sufficient to establish that the unexpected benefits of co-administering ezetimibe and aspirin is reasonably commensurate with the full scope of the claim. Claim 1 is directed to a composition which comprises ezetimibe and aspirin in a range of amounts. Applicants presented data showing that rats treated with a combination of ezetimibe and aspirin experienced AA induced platelet aggregation far greater than rats treated with either aspirin or ezetimibe alone. (See, e.g., December 4, 2007 Response, pages 3-6). Referring directly to these results, Dr. Davis states that "these results indicate that the combination of ezetimibe with aspirin synergistically and unexpectedly enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent acting alone." (Davis Declaration at paragraph 6). Support for the specific range of doses recited in the claims is found in the Declaration of Dr. Chintala, which states that the therapeutic range for aspirin is between 1 and 1000 mg and ezetimibe doses of between 0.1 and 1000 mg/day would be effective in humans. (Chintala Declaration at paragraphs 7 and 9).

Testing across the entire claimed dose ranges is not believed to be necessary because the observed synergistic effect is not dependent on the amount of each compound present. As the presented evidence establishes, co-administering ezetimibe with aspirin will enhance the platelet aggregation effect to a greater extent than either of these compounds

acting alone. Applicants have not contended that this effect is somehow dependent on the exact concentration or amount of either compound administered. Stated another way, regardless of the amount of ezetimibe and aspirin administered to a subject, the platelet aggregation effect would be greater if the compounds were co-administered than if they were administered individually. Though only one specific value is tested, one of ordinary skill in the art would be able to view this evidence and extend the probative value thereof to the full scope of the claim. "'[C]ommensurate in scope' means that the evidence provides a reasonable basis for concluding that the untested embodiments encompassed by the claims would behave similarly to the tested embodiment(s)." *Ex Parte Lee*, 2007 WL 1766990 (BPAI, June 19, 2007) (citing *In re Linder*).

Upon a presentation of unexpected results, the burden remains on the Examiner to show why this evidence would not be commensurate in scope with the claims. See *In re Rinehart*, 189 USPQ 143, 147 (USPQ 1976). While the Office Action attempts to satisfy this burden by pointing to studies showing that the aspirin dosage is dependent on the specific patient population being tested, this showing does not appear relevant to establish that the synergistic effect of co-administering ezetimibe and aspirin would not be observed across the claimed dosage range. Applicants' data shows that ezetimibe synergistically enhances the ability of aspirin to inhibit platelet aggregation, and it is reasonable to assume that the therapeutic range of aspirin is between 1 and 1000 mg, which represents the range recited in claim 1. (Chintala Declaration at paragraph 7). The behavior of a composition comprising ezetimibe and aspirin within the claimed range would not necessarily change simply because some patients may require a larger dosage of one compound or the other. The synergistic effect on platelet aggregation would remain.

Consequently, because the evidence presented establishes that a synergistic effect would be expected for the scope of aspirin and ezetimibe recited in the claims, Applicants respectfully assert that their showing of unexpected results supports a finding of nonobviousness.

CONCLUSION

Accordingly, Applicants respectfully request that the § 103(a) rejections be reconsidered and withdrawn and claims 1, 3, 35-37, 42, 45, and 47 be allowed.

Respectfully submitted,

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